Memory is not enough: the neurobiological substrates of dynamic cognitive reserve

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Memory is not enough: the neurobiological substrates of dynamic cognitive reserve.

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Running title: Dynamic cognitive reserve in AD

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Abstract

Changes in the residual memory variance are considered as a dynamic aspect of cognitive reserve (d-CR). We aimed to investigate for the first time the neural substrate associated with changes in the residual memory variance overtime in patients with a-MCI. Thirty-four a-MCI patients followed-up for 36 months and 48 healthy elderly individuals (HE) were recruited. All participants underwent 3T MRI, collecting T1-weighted images for voxel-based morphometry (VBM). They underwent an extensive neuropsychological battery, including six episodic memory tests. In patients and controls separately, factor analyses were used on the episodic memory scores to obtain a composite memory score (C-MS); Partial Least Square analyses were used to decompose the variance of C-MS in latent variables (LT scores), accounting for demographic variables and for the general cognitive efficiency level; linear regressions were applied on LT scores, striping off any contribution of general cognitive abilities, to obtain the residual value of memory variance, considered as an index of d-CR. LT scores and d-CR were used in discriminant analysis, in patients only. Finally, LT scores and d-CR were used as variable of interest in VBM analysis. The d-CR score was not able to correctly classify patients. In both, a-MCI patients and HE, LT^{1st} and d-CR scores showed correlations with GM volumes in common and in specific brain areas. Using CR measures limited to assess memory function is likely less sensitive to detect the cognitive decline and predict AD evolution. In conclusion, dynamic CR needs a measure of general cognition to identify AD conversion efficiently.

Keywords:

Dynamic cognitive reserve; Mild cognitive impairment; memory; voxel-based morphometry

Introduction

Cognitive reserve (CR) is a theoretical framework used to explain the different individual resilience to neurodegeneration [1]. Two different underling mechanisms have been hypothesised, the *neural reserve*, which postulates that each individual can accumulate variable resources that determine individual performance also in the absence of pathology, and the *neural compensation* that makes the brain better able to cope or compensate for brain damage [1]. Several previous studies investigated the effect on brain resilience of CR due to the lifestyle enrichment [1-5]. The majority of these studies used static measures of CR [6], such as years of formal education [1-5], or occupational attainment [4]that do not allow the changes in the patients' cognition to be specifically assessed. In addition, these static measures are imprecise because they may relate to cognitive performance for reasons other than the reserve mechanisms [6]. For instance the same level of education or of occupational attainment does not reflect the same experience in all individuals [7].

Moreover, CR is modifiable throughout life and previous studies reported that high level of leisure activities performed during life, whether cognitive, social and also physical, reduce the risk of developing dementia [1,3-4]. More targeted studies investigated, both in patients with AD [6-7] and in healthy elderly [8,9], the CR measured in terms of changes in memory functions. All these previous studies [6-9] quantified CR as residual variance of memory scores, after accounting for demographical and brain damage variables. The residual method is in line with a definition of CR [7] as discrepancy between observed performance and expected level of performance. Therefore, individuals who perform better than predicted show positive residual score. It means that they have high CR. Conversely, subjects who perform worse than predicted show negative residual score and they have low CR. The residual variable (expressing the CR) differs from the observed score (in this case quantified as memory performance) because any variance related to demographics, brain damage and cognitive efficiency was

ruled out, in addition to error. To conceptualize CR in terms of residual variance of memory functions made the CR's concept more flexible and adaptable to cognitive changes. It involves a more dynamic concept of CR that fits better than the more "static" measures based on education or lifestyle indicators with the cognitive changes due to aging and neurodegeneration.

However, in most of these studies, brain pathology (in terms of white matter hyperintenisites, hippocampal or total intracranial volumes, etc.,) was factored out as part of the composition of memory variance [6-7,9]. To our knowledge no previous study investigated directly the relationship between CR considered as residual variance of memory scores over time and regional grey matter volumes changes in AD patients at pre-dementia stage. For this purpose we recruited a cohort of amnestic mild cognitive impairment due to AD patients and used the actual and previous memory performances as a measure of dynamic CR (d-CR). Moreover, we investigated the potential association between this measure of d-CR and regional gray matter volume changes by using the voxel-based morphometry technique (VBM) [10]. VBM is an unbiased method of image analysis that has strongly contributed in clarifying the relationship between regional patterns of grey matter (GM) atrophy and specific neuropsychological features observed in AD patients at various clinical stages [11-13]. One of the most remarkable strengths of VBM is to allow, with no *a priori* hypotheses on specific anatomical localizations of damage, to test for associations between individual regional brain abnormalities and correspondent measures of cognitive impairment. This is extremely valuable when investigating neurological conditions, such as degenerative dementias, which are characterized by diffuse brain tissue damage.

In this study, using VBM and the pathological model of AD, we aimed at assessing the role of dynamic CR over time and regional grey matter changes. Moreover, we aimed at assessing the classification power in Converters and Non-Converters of the dynamic CR index.

Material and Methods

Subjects

A cohort of 34 consecutive patients diagnosed as suffering from a-MCI according to current criteria [14-15] were recruited and followed-up for 3 years. By definition, all patients had to report subjective memory impairment as clinical onset, corroborated by an assistant and confirmed by performances below the normality cut-off scores on at least one of the administered tests for episodic memory (see below). In addition, patients had to show performances above the cut-off of normality in all other administered test (see below).

All patients had to fulfil the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [16] criteria for the diagnosis of minor neurocognitive disorders. They had to show normal scores adjusted for age and education at the Mini Mental State Examination (MMSE) [17] [Italian adjusted cut-off score$\geq$23.8 [18]; this means that patients with a MMSE score equal or lower than 23.7 were excluded, while patients with MMSE score equal or higher than 23.8 were included]. Moreover, patients' impairment had to result in no or in a very mild impact on daily living activities, as confirmed by a total Clinical Dementia Rating score [19] not exceeding 0.5. Patients with a Hachinski score [20] higher than 5 were excluded. All patients underwent an extensive neuropsychological battery and MRI scanning. In order to improve the diagnostic accuracy, conventional MRI was clinically reviewed by using the Medial Temporal lobe Atrophy scale (MTA) [21] to include only patients with a MTA score > 1 (MTA mean score: 2.1$\pm$1.0). This means that only patients with MCI-due to AD at intermediate likelihood were included for the study [14,15]. In the present study we used a longitudinal design following up all patients for 36 months. At the follow-up visit, all patients underwent clinical, neuropsychological and MRI evaluation in order to re-classify them as Non-Converters or Converters to AD. The diagnosis of AD was in accordance with the clinical criteria established by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [22].

A group of 48 healthy elderly individuals (HE) were also recruited and they underwent a neuropsychological assessment and MRI acquisition. HE had to show MTA score <1, MMSE score $\geq$ 27 and no evidence of cognitive impairment (see below the Neuropsychological assessment section) to be included in the study. All subjects (patients and controls) enrolled in the study, were screened for major systemic, psychiatric, and other neurological illnesses. Finally, to reduce any potential source of variability due to hemispheric dominance, all subjects had to be right-handed as assessed by the Edinburgh Handedness Inventory (EHI; cut-off score for right handiness $\geq$ 6) [23]. Participants' EHI scores ranged from 8 to 12.

The principal demographic and clinical characteristics of all participants are summarized in Table 1.

Please insert Table 1 around here

The study was approved by the Ethical Committee of Santa Lucia Foundation and written informed consent was obtained from all participants before study initiation. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Neuropsychological assessment.

All recruited patients underwent an extensive neuropsychological battery including the following tests at both baseline and at follow-up visits: Verbal episodic long-term memory: 15-Word List (Immediate and 15-min Delayed recall)[24] and hit and false rates in Recognition test; Short Story test (Immediate and 20-min Delayed recall) [25]; Visuo-spatial episodic long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall) [25]; Short-term memory: Digit span and the Corsi Block Tapping task forward and backward [26]; Executive functions: Phonological Word Fluency [24] and

Modified Card Sorting Test [27] ; Language: Naming objects subtest of the BADA ("Batteria per l'Analisi dei Deficit Afasici", Italian for "Battery for the analysis of aphasic deficits") [28]; Reasoning: Raven's Coloured Progressive Matrices [24]; Constructional praxis: Copy of simple drawings [24] and Copy of drawings with landmarks [24]; Copy of Complex Rey's Figure [25].

Healthy elderly individuals underwent the same extensive neuropsychological battery only at the time of recruitment.

For the specific purpose of the present study we only consider the performance obtained at memory tests (see Table 2). Moreover, the memory scores were not adjusted for age, gender and education, but all these demographic variables were used as covariates of no interest in the in the following steps of the analysis as detailed below.

Six one-way ANOVAs (with age, education and sex as covariate of no interests) were used to assess between-groups differences separately at baseline (a-MCI vs. HE) and at follow-up (Converters vs. Non-Converters) in memory tests. To avoid the type-I error Bonferroni's correction was applied (p value threshold $\alpha = 0.05/6 = 0.008$).

Dynamic CR index computation

Statistical analyses were carried out in SPSS 21 (http://www-01.ibm.com/software/it/analytics/spss/).

Amnestic mild cognitive impairment patients

As illustrated in the flowchart (Figure 1 panel A) to obtain in a-MCI patients an index of dynamic CR from available verbal episodic memory scores we performed a series of factorial and regression analyses. First, to obtain a single index of memory expressing both the baseline amount of memory and the longitudinal changes, factor analyses were performed. Factor analysis describes variability among observed correlated variables in terms of a potentially lower number of unobserved variables called factors. In the present case we hypothesized that the factors represented the common variance in the individual memory performance during 36 months. Specifically, 15-Word List Immediate recall (W-IR),

15-Word List Delayed recall (W-DR), 15-Word List Recognition Hit-Rates (W-HR), 15-Word List Recognition False (W-F), Short Story test Immediate (SS-IR) and Short Story test Delayed recall (SS-DR) scores entered as variables of interest in two different factor analyses (the former using baseline memory scores and the latter using follow-up memory scores, respectively). Factor analyses were performed using the Maximum Likelihood estimation method (with eigenvalues >1 for the factors' extraction, and VARIMAX method for factors' rotation). Factors extracted from baseline and follow-up memory scores were averaged to create a composite factorial memory score (defined as C-MS). The C-MS expressed in a-MCI patients the resilience to decay of episodic long-term memory store.

Partial least squares regression (PLS) was used to regress from C-MS (set as Y, the dependent variable) all the confounding variables (Xs , the independent variables) that might explain part of the C-MS' variance. PLS is a statistical method for constructing predictive models (to predict Y from X) when the factors are many and highly collinear. PLS is used when although many manifest factors can be hypothesized, there are only few underlying or latent factors that account for most of the variation in the response. The general idea of PLS is to try to extract these latent factors (that are part of the variance of the X), accounting for as much of the manifest factor variation as possible while modelling the responses well. For this reason, the acronym PLS has also been taken to mean ‘‘projection to latent structure.’’ In the present case demographic variables (age at any time-point visit, gender and years of formal education) and general cognitive efficiency (as measured by MMSE at any time-point visit) entered in the PLS analysis. Therefore, variance in the C-MS was decomposed into orthogonal latent factors. The minimum number of latent factors (named latent scores, LTs) explaining the maximum variance of C-MS was retain for further analyses. Moreover, the Variable Importance in the Projection index (VIP index) was used to assess the contribution of each considered variable in the composition of C-MS's variance into the latent scores. Finally, the variables showing the highest VIP were regressed from the latent scores using the linear regression model. The residual value of variance in memory performances, remaining

after accounting for all nuisance variables, was considered as an index of dynamic CR (d-CR). The LTs and the d-CR index were used as variables of interest in the MRI data analyses.

Insert Figure 1 around here

Classification of a-MCI-due to AD patients in Converters and Non-Converters based on latent scores and d-CR index.

For such a classification, two multiple discriminant analyses were employed only in a-MCI patients, in which, individual follow-up outcomes (Converter/Non-Converters) were entered as grouping variable. In the first analysis latent scores (LTs) derived from PLS and the individual values of the MTA scale were used as predictors; in the second analysis the d-CR index and, again, the individual values of the MTA scale were used as predictors.

Healthy elderly individuals

In the HE group we performed the same statistical analyses (factor analysis, creation of the composite factorial memory score, PLS analysis, linear regression analysis) with the only exception for the discriminant analysis (see Figure 1 Panel B). Moreover the episodic verbal memory scores (W-IR, W-DR, W-HR, W-F, SS-IR and SS-DR) were entered as variables of interest in the factor analysis only once (at time of recruitment). As a consequence, the residual memory variance extracted by linear regression on PLS's LT scores did not express the longitudinal changes in the memory functions but only the current memory warehouse in the HE group. For this reason we named this index as residual memory warehouse (r-MW) index. As for a-MCI patients the LT scores and the r-MW index were used as predictors in the MRI analysis.

MRI acquisition

All a-MCI patients and HE underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany), including the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR=6190 ms, TE=12/109 ms); 2) fast-fluid attenuated inversion recovery (FLAIR) (TR=8170 ms, TE=96 ms, TI=2100 ms); 3) 3D-Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256x224, n. slices=176, thickness=1 mm). According to the inclusion criteria, TSE and FLAIR scans were reviewed to exclude the presence of remarkable macroscopic brain abnormalities, as previously described [11].

Whole brain VBM analysis and statistics

None of the T1-weighted (MDEFT) volumes were affected by macroscopic artefacts, as assessed by visual examination.

T1-weighted volumes were pre-processed using the VBM protocol [48-49] implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), which consists of an iterative combination of segmentations and normalisations to produce a GM probability map [10,29] in standard space (Montreal Neurological Institute, or MNI coordinates) for every subject. In order to compensate for compression or expansion which might occur during warping of images to match the template, GM maps were "modulated" by multiplying the intensity of each voxel in the final images by the Jacobian determinant of the transformation, corresponding to its relative volume before and after warping [29]. GM, WM and CSF volumes were computed from these probabilistic images for every subject. All data were then smoothed using a 12-mm FWHM Gaussian kernel.

Statistical analysis of regional GM volumes were performed on smoothed GM maps within the framework of the general linear model. A one-sample T-test was employed to assess correlations between LT scores, d-CR index and regional GM volumes in a-MCI patients. Moreover we assessed correlations between LT scores, r-MW and regional GM volumes also in HE group. All analyses were

run whole-brain (i.e., with no a priori hypothesis on anatomical localisation of findings). Intracranial volume (obtained by adding up WM volume +GM volume + CSF volume) was always entered in all analyses as covariate of no interest. Results were accepted as significant at p values<0.05 FWE corrected at cluster level.

Results

Demographic and clinical characteristics of studied subjects

As reported in Table 1 there were no statistical differences at baseline between a-MCI patients and HE group in mean age ($F_{1,80}$=1.4, p= 0.25), or gender distribution (Chi-square Yates corrected=0.5, df=1, p= 0.49). Conversely, there were significant differences in the years of formal education ($F_{1,80}$=5.1, p= 0.02), and in the MMSE score ($F_{1,80}$=33.6, p< 0.001). At follow-up, 15 out of 34 a-MCI patients (44.0%) converted to AD (Converters), while 19 out of 34 (56.0%) remained a-MCI (Non-Converters). There were no differences between Converters and Non-Converters in mean age ($F_{1,32}$=0.1, p= 0.78) or years of formal education ($F_{1,32}$=1.9, p= 0.18.). Conversely, we found significant differences in the gender distribution (Chi-square Yates corrected=4.7, df=1, p= 0.03) and as expected at MMSE score ($F_{1,32}$=32.1, p<0.001).

Verbal episodic long-term memory assessment

Panel A of Table 2 summarizes the memory performance of patients with a-MCI compared to controls at baseline. As expected, a-MCI patients showed significantly lower scores than HE at all tests assessing the verbal episodic long-term memory (W-IR: $F_{1,80}$=52.1, p<0.001; W-DR: $F_{1,80}$= 94.5, p<0.001; W-HR: $F_{1,80}$=34.1, p<0.001; W-F: $F_{1,80}$=9.5, p=0.003; SS-IR: $F_{1,80}$=14.5, p<0.001; SS-DR: $F_{1,80}$=19.4, p<0.001). Moreover, panel B shows memory performances obtained by a-MCI patients classified based on their clinical evolution. Converters showed significantly lower scores than

Non-Conversers in the W-ID ($F_{1,32}$=20.7, p<0.001) and in the W-DR ($F_{1,32}$=9.17, p=0.005). No other differences were detected.

Amnestic mild cognitive impairment patients

Factor analyses

As reported in Figure 2 (and in the Supplementary Table 1) from the initial six verbal episodic memory scores entered in the analyses, two factors were extracted for baseline (55.6 % of variance) (Figure 2, panel A) and others two factors were extracted for follow-up (67.4% of variance) visit (Figure 2, panel B). In both cases the Goodness-of-fit test were not significant (Baseline: Chi-square 6.53, df=4, p=0.16; Follow-up: 7.74, df=4, p=0.10, respectively), revealing that the extracted factors are a good description of the data. Specifically, the Communalities (Supplementary Table 2) showed that the factors extracted explained almost totally the variance of the delayed recall measures (W-DR and SS-DR, respectively) followed by the variance of the immediate recall measures (W-IR and SS-IR, respectively). Moreover, correlations' coefficients between verbal episodic memory scores and factors extracted were also reported both for baseline and follow-up (see Rotated Factor Matrix in the Supplementary Table 2). The highest correlations were observed between SS-IR (r=0.80) and SS-DR (r=0.98) with factor 1 and between W-DR (0.95) and factor 2 for memory measures obtained at baseline (Supplementary Table 2). High correlations were also observed between SS-IR (r=0.85), SS-DR (r=0.98) and W-DR (r=0.72) with factor 1, and finally between W-HR (r=0.78) with factor 2 (see Supplementary Table 2).

As reported in the Methods the C-MS was created by averaging the four extracted factors (Factor 1 and Factor 2 both for baseline and follow-up, respectively) and it was used in the Partial Least Squares analysis.

Partial Least Squares and linear regression analyses

Five latent variables were extracted by PLS, as reported in the Figure 2, panel C (see also Supplementary Table 3). The first latent variable (LT^{1st}) explained the most of the covariance of X and Y (36.0% in both cases) therefore it was retained for further analysis.

Moreover, the LT^{1st} was significantly different (t=-2.87, df=32, p=0.007) in Converters (mean$\pm$ SD: -0.74$\pm$1.1) compared to Non-Converters (mean$\pm$ SD: 0.59$\pm$1.5).

The VIP index (Figure 2, panel D) and the loadings (see also Supplementary Table 3) revealed that the MMSE scores at baseline contributed for the mostly in the composition of LT^{1st} variance. Therefore MMSE scores at baseline were regressed again from the LT^{1st}. According to the Methods, the residual values of the LT^{1st} was considered a proxy of dynamic CR (d-CR). However, no significant difference was found in the mean of d-CR index (t-0.66, df=32, p=0.51) between Converters (mean$\pm$ SD: -0.03$\pm$0.2) and Non-Converters (mean$\pm$ SD: 0.03$\pm$0.3).

Insert Figure 2 around here

Discriminant analysis

The LT^{1st} showed the highest discriminatory power for patients' conversion to AD (Wilks's lambda= 0.78, F=8.47, p<0.007; 73.3% sensitivity; 63.2% specificity; 67.6% accuracy). Conversely, when only d-CR index was considered in the analysis, it showed a modest ability to correctly classify patients (53.3% sensitivity; 57.9% specificity; 55.9% accuracy).

MRI

VBM correlation analyses

As shown in Figure 3 the VBM correlation analysis in patients revealed a significant direct association between LT^{1st} scores and between d-CR index and regional GM volumes, respectively.

When considering LT^{1st} scores as variable of interest (in green in Figure 3) we found significant

correlations with GM volumes in widespread brain areas involving bilaterally anterior cingulate cortex (ACC, BA32), Posterior Cingulate Cortex (PCC, BA31) precuneus (BA7), hippocampus, perirhinal, entorhinal and parahippocampal gyrus (BAs28, 35 and 34), insular cortex and extensively the cerebellum (mainly Crus-I, Lobule-VII).

When considering the d-CR index we found significant correlations with regional GM volumes in several brain areas. A part of these brain areas were the same observed in the previous analysis (the overlapped areas are shown in yellow in the Figure 3). Conversely, we found also a specific association (in red in Figure 3) mainly in the bilateral posterior middle part of the ACC (pm-ACC), in the superior frontal gyrus bilaterally (BA8), in the right orbitofrontal cortex (BA47), in the right superior temporal gyrus (BA22). It is remarkable that the LT^{1st} (which accounts for general cognitive abilities rather than memory alone) correlated more extensively than the d-CR index with the right hippocampus.

Insert Figure 3 around here

Healthy elderly individuals

Factor analysis

Also for the HE group two factors were extracted (Figure 4, panel A and Supplementary Table 4), accounting for 61.21% of variance (Goodness-of-fit test: Chi-square=0.09, df=4, p=0.999). Communalities (see Supplementary Table 4) revealed that the factors explained for a 98% the variance of the immediate recall of the Short Story test (SS-IR), and then the variance of the delayed recall of the Short Story test (SS-DR) and finally of the immediate and delayed recall of the 15-Word List. Supplementary Table 4 reported also the correlations' coefficients between verbal episodic memory scores and two factors extracted (see the Rotated Factor Matrix). Factor 1 showed highest correlations with W-IR (r=0.88) and with W-DR (r=0.82). Conversely, Factor 2 showed highest correlation with the

Short Story test (SS-ID: r=0.99, and SS-RD: r=0.88, respectively).

Again, the C-MS was created by averaging the two extracted factors, and it was used in the PLS analysis.

Partial Least Squares and linear regression analyses

As reported in Figure 4, panel B (see also Supplementary Table 5), four latent variables were extracted by PLS analysis, and, also in this case, the LT^{1st} explained the most of the variance (40% for X and 22% for Y, respectively). The VIP index Figure 4, panel C and the loadings (see also Supplementary Table 5) revealed that MMSE score was the main contributor to the composition of LT^{1st}'s variance also for the HE group. Again MMSE scores was regressed from LT^{1st} producing the residual LT^{1st} value considered as r-MW. Finally, as stated in the Methods, residual LT^{1st} and r-MW scores were used as variable of interest in the MRI analyses.

Insert Figure 4 around here

MRI

VBM Correlation analyses

In HE group we found a significant positive association between LT^{1st} scores (in green in Figure 5) and regional GM volumes involving mainly orbito-frontal cortex (BA47), ACC (BA32), PCC (BA31), precuneus (BA7), premotor cortex (BA6), insula, fornix and the thalamus bilaterally. We found also an association with the left amygdala and the hippocampus and with cerebellum (mainly the lobule VI bilaterally). When considering the r-MW index we found an overlap (in yellow in Figure 5) with the bilateral BA6, in the left amygdala, the bilateral thalamus, and finally in the bilateral ACC (BA32) and in the left orbito-frontal cortex (BA47). Conversely, we found specific association between r-MW index (in red) and GM volumes only in the left dorsolateral prefrontal cortex (BA46) and in the most medial part of the BA6 bilaterally.

Discussion

In the present study we investigated the neural substrates underlying different levels of CR assessed by dynamic measures. Previous studies demonstrated that latent variables extracted from the decomposition of memory variance (accounting for demographic and brain-structural variables) could be used as a useful measure of CR [6,7], and that changes in the residual memory variance captured the dynamic aspects of CR [9]. However, this is the first study investigating the relationship between regional GM changes and dynamic aspect of CR in patients with a-MCI and in healthy elderly.

In particular, we assessed both in patients and controls, the association with brain tissue changes and two different measures of dynamic CR, the LT^{1st} and the d-CR (or r-MW) scores, separately.

We were interested in assessing the interplay between CR and AD neuropathology, therefore we recruited patients with a-MCI-due to AD at an intermediate likelihood [14,15] as documented by both episodic memory and by MTA scores. Conversely, HE group has been recruited to have no clinical evidence of AD neuropathology.

There were no between-group differences in demographical features with the only exception of the educational level. Therefore we investigated separately the groups of a-MCI and of HE. As expected, patients with a-MCI (considered as a whole) showed worse performances than HE in each administered memory test. Moreover, when divided a-MCI sample as Converters and Non-Converters, the former showed worse scores than the latter at follow-up.

We created indexes of dynamic CR from available verbal episodic memory scores performing a series of factorial and regression analyses. These indexes were used to investigate potential association with GM volumes by VBM.

We observed a high correlation between the factors extracted using the factor analyses and the immediate and the delayed recall scores, both in patients and in HE groups. We speculated that the factors extracted,

and the derived C-MS, may be considered a good concise representation of the observed variables (the episodic memory scores). Therefore, we used the PLS to extract the LT scores underlying the C-MS,. Specifically, we obtained that the first LT (the LT^{1st}) explained most of the variance, reflecting the maximum common variance of the episodic memory factors (measured as C-MS). Both in a-MCI and HE groups the PLS analysis showed that the MMSE scores contributed significantly in the composition of LT^{1st} scores (as measured by the VIP index). This means that the variance of the C-MS included, at least in part, the variance due to the level of general cognitive efficiency. In the present case, the CR considered in terms of latent variable, derived from the C-MS, is conceptualised as variance formed both by episodic memory and by the general cognition scores. Therefore, the CR index did not express uniquely the changes in memory performances but the general cognitive changes occurring during 36 months. As a consequence, to obtain a CR index expressing changes in the variance of the episodic memory only, general cognitive efficiency scores were regressed again from LT^{1st} scores. The d-CR index obtained was considered as a "pure" measure of dynamic changes in episodic memory.

The present study showed that LT^{1st} and d-CR scores were not equivalent to express the CR.

It is remarkable that when considering the CR's scores (LT^{1st} and d-CR scores) in a-MCI patients divided according their clinical profile in Converters and Non-Converters we observed significant difference only for the LT^{1st} scores. Indeed, Converters showed significantly negative LT^{1st} scores compared to Non-Converters that showed positive LT^{1st} scores. We hypothesised that only in Converters group, when memory performance worsens, the relative weight of the level of general cognitive efficiency (as measured by the MMSE scores) significantly increase in explaining the total variance of the C-MS. Conversely, we did not observe this trend when comparing Converters and Non-Converters in the d-CR score. In other words, when memory performance worsens the ability to synergistically use the other cognitive functions, different from memory, permits to withstand cognitive decline. Moreover, LT^{1st} scores were the best predictors for patients' conversion to AD in the discriminant analysis. Conversely,

d-CR index showed only a modest ability to correctly classify patients.

When considering the neuroimaging analyses in a-MCI, LT^{1st} and d-CR scores showed correlations with GM volumes both in the common and in the specific brain areas. In particular, in a-MCI patients, common areas of correlations were found with the GM volumes in the part of the ACC (BA32), in the part of the PCC (BA31), in the insula bilaterally, in the left hippocampus and parahippocampal gyrus. We speculated that the common brain areas we observed are likely involved both in the memory and in the more general cognitive efficiency processes. Effectively these areas are known to be involved in the encoding an in the retrieval of episodic memory processes [30,31] as well as in more general strategic abilities [32].

On the contrary, specific correlations were observed between LT^{1st} scores and the bilateral precuneus (BA7), the right hippocampus and parahippocampal gyrus and with cerebellum. Previously in AD patients we reported both that atrophy in the precuneus was related to cognitive deficits [33] and that functional changes into the precuneus were the best predictor of conversion from MCI to AD in short time [33]. In addition, more recently [5] we found in a-MCI patients with high CR, compared with those low CR, an increased functional connectivity in a network involving the precuneus, and decreased connectivity in a fronto-temporo-cerebellar network. This study suggested the presence of compensative mechanisms that allow the a-MCI patients with high CR to cope better with neurodegenerative process [5].

The d-CR index correlated specifically with the posterior part of the middle ACC (pm-ACC), in the superior frontal gyrus bilaterally (BA8), in the right orbitofrontal cortex (BA47), in the right superior temporal gyrus (BA22). The pm-ACC has been found to relate with a rapid cognitive response [34], not reflecting the correctness of the response but the cognitive activation only. Nevertheless the right orbitofrontal cortex (BA47) is typically related to the go-no-go tasks [35] and atrophy in this brain area may be lead to the inhibition deficits. We hypothesised that the patients reaching positive values in the

d-CR index (and consequently high CR) showed more cognitive promptness, but not necessary more accuracy in the response (as typically observed in patients with low CR). This inhibition's deficit might account for the significant difference observed in the a-MCI patients compared to HE group in the false responses of the recognition test.

Also in the HE group there were overlapping areas of correlation between GM volumes and LT^{1st} and r-MW scores mainly in the bilateral ACC (BA32), in the supramarginal gyrus (BA6), in the thalami, and in the left orbito-frontal cortex (BA47). However, the LT^{1st} scores associated specifically with the orbito-frontal cortex (BA47), with the PCC (BA31), precuneus (BA7), with the insula and cerebellum bilaterally. Conversely, r-MW was specifically associated with GM volume only in the left dorso-lateral prefrontal cortex (BA46) and in the most medial part of the BA6. Some of these areas were the same observed also in the a-MCI patients (BAs7, 31, 32, 47, cerebellum) but others, such as thalamus and insula bilaterally, were found associated with CR scores only in the HE group. A previous study showed these brain regions to be altered in healthy elderly according to their CR level [36] suggesting the existence of a compensatory network that is used to maintain function in the face of age-related physiological changes. Although we did not perform a formal comparison of the association between GM volume and the scores derived by our analysis between a-MCI and HE, qualitatively we observe that LT^{1st} is mainly associated, in both groups, with the volume of PCC/precuneus and ACC. Conversely the residual score (d-CR in a-MCI and r-MW in HE) was mainly associated with the volume of the most anterior portion of ACC. These overlapping results confirm that the integrity of the cingulate cortex is crucial for cognitive efficiency.

In conclusion this study shows that indices of dynamic CR that strip off any contribution of general cognitive abilities to retain exclusively memory processes are not able to identify the conversion to AD efficiently. Therefore the integrity of memory function is not sufficient to withstand neurodegeneration. By contrast, the ability to use synergistically the different cognitive functions is protective against the

conversion to AD. Using CR measures limited to assess only memory function is likely less sensitive to detect the cognitive decline and to predict patients' conversion. Based on current results, we propose, in clinical settings, the use of proxy-measures of dynamic CR that include also some weighting for the level of general cognition. Future studies of standardization are needed to define appropriate instruments for clinical use.

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Conflict of interests

None of the Authors has any conflict of interest to disclose.

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Figure Legends

Figure 1. Flowchart in a-MCI patients and healthy elderly individuals

In panel A is shown the statistical flowchart applied to obtain the dynamic cognitive reserve index (d-CR) in a-MCI group. The d-CR index was used both for discriminant and for voxel-based morphometry (VBM) analyses. Panel B shows the statistical flowchart applied to obtain the residual memory warehouse index (r-MW) in healthy elderly group. The r-MW index was used for voxel-based morphometry (VBM) analyses. See text for further details.

Abbreviations: d-CR=dynamic cognitive reserve index; r-MW= residual memory warehouse index; VBM= voxel-based morphometry.

Figure 2. Results of factor and partial least square analyses in patients with a-MCI.

There are shown here eigenvalues and percentage of variance for the six extracted factors at baseline (Panel A) and follow-up (Panel B). In bold characters there are reported the most important eigenvalues that identify Factor 1 and Factor 2, which explain most of the variance of the six episodic memory scores considered in the factor analyses. Panel C shows the result of PLS analysis. The first latent variable (LT^{1st}) explain most of the covariance of X and Y (36.0% in both cases). Panel D shows the result of the Variable Importance in the Projection index (VIP index) relatively to the (LT^{1st}). VIP index identifies the MMSE score at baseline, as variable that contributed the most to the composition of C-MS's variance into the LT^{1st}. See text for further details.

Abbreviations: a-MCI= amnestic mild cognitive impairment; C-MS= composite memory score; MMSE= Mini mental State Examination; LT^{1st}= the first latent variable; PLS= partial least square; VIP= Variable Importance in the Projection index; λ=eigenvalue.

Figure 3. Correlations between Latent scores, d-CR index and regional GM volumes in a-MCI

patients

The VBM correlation's analyses in a-MCI patients revealed a significant direct association between LT^{1st} scores and d-CR index with regional GM volumes, respectively. The correlations between GM volumes with the LT^{1st} scores are shown in green, with the d-CR are shown in red, and the overlaps are shown in yellow. See text for further details.

Abbreviations: VBM= voxel-based morphometry; a-MCI= amnestic mild cognitive impairment; LT^{1st}= the first latent variable; d-CR= dynamic cognitive reserve; GM= grey matter.

Figure 4 Results of factor and partial least square analyses in healthy elderly individuals.

Panel A shows eigenvalues and the percentage of variance for the six extracted factors in the HE group. In bold characters there are reported the most important eigenvalues that identify Factor 1 and Factor 2, which explain most of the variance of the six episodic memory scores considered in the factor analyses. In panel B is shown the result of the PLS analysis. The first latent variable (LT^{1st}) explain most of the covariance of X and Y (40.0% for X and 22.0% for Y). Panel C shows the result of the Variable Importance in the Projection index (VIP index) relatively to the (LT^{1st}). VIP index identifies, also in the HE group, the MMSE score as variable that contributed most to the composition of C-MS's variance into the LT^{1st}. See text for further details.

Abbreviations: C-MS= composite memory score; HE= healthy elderly individuals; MMSE= Mini mental State Examination; LT^{1st}= the first latent variable; PLS= partial least square; VIP= Variable Importance in the Projection index; λ=eigenvalue.

Figure 5. Correlations between Latent scores, r-MW index and regional GM volumes in healthy elderly individuals

The VBM correlation's analyses in HE group revealed a significant direct association between LT^{1st} scores and r-MW index with regional GM volumes, respectively. The correlations between GM volumes

with the LT^{1st} scores are shown in green, with the r-MW are shown in red, and the overlaps are shown in yellow. See text for further details.

Abbreviations: VBM= voxel-based morphometry; HE= healthy elderly; LT^{1st}= the first latent variable; r-MW=residual memory warehouse; GM= grey matter.

Table 1. Demographic and clinical characteristics of studied subjects.

Baseline	**a-MCI**	**HE**	**p-level**
	N=34	**N=48**	
Mean (SD) age [years][a]	70.9 (7.9)	69.2 (6.1)	0.246
Gender (F/M)[b]	19/15	20/24	0.361
Mean (SD) years of formal education[a]	10.5 (4.3)*	12.5 (3.7)	0.026
Mean (SD) MMSE score[a]	26.9 (2.0)*	28.9 (1.1)	0.000
Follow-up	**Converters**	**Non-Converters**	
	N=15	**N=19**	
Mean (SD) age [years][a]	73.6 (6.8)	72.9 (8.7)	0.784
Gender (F/M)[b]	12/3#	7/12	0.011
Mean (SD) years of formal education[a]	9.4 (4.2)	11.4 (4.4)	0.181
Mean (SD) MMSE score[a]	21.5 (5.4)#	28.0 (2.2)	0.000

[a] One-way ANOVA; [b] Chi-square Yates corrected.

Post-Hoc comparison: * a-MCI vs HE $p<0.05$; # Converters vs. Non-Converters $p<0.05$;

Abbreviations: a-MCI= amnestic Mild Cognitive Impairment; HE=healthy elderly individuals. MMSE=mini mental state examination; For each group of subjects, the table shows the mean (SD) of age, years of formal education, MMSE and gender distribution.

Table 2. Memory performances obtained by patients with a-MCI compared with healthy elderly at baseline and by patients at follow-up

A) Baseline				
Domain	**Test**	**a-MCI**	**HE**	**p-level**
Verbal episodic long-term memory				
	W-IR	26.3 (7.1)*	40.4 (9.6)	0.000
	W-DR	3.1 (2.4)*	8.2 (2.3)	0.000
	W-HR	10.0 (3.0)*	13.4 (1.6)	0.000
	W-F	3.8 (3.7)*	1.6 (1.8)	0.002
	SS-IR	3.4 (1.8)*	5.6 (1.4)	0.001
	SS-DR	3.2 (2.5)*	5.5 (1.3)	0.000
B) Follow-up				
Domain	**Test**	**Converters**	**Non-Converters**	
Verbal episodic long-term memory				
	W-IR	18.6 (6.6)#	32.3 (10.0)	0.001
	W-DR	1.3 (1.5)#	3.8 (2.9)	0.004
	W-HR	8.3 (5.3)	11.1 (2.7)	0.065
	W-F	9.4 (9.0)	3.4 (4.1)	0.020
	SS-IR	3.0 (2.7)	5.4 (1.3)	0.012
	SS-DR	1.0 (2.2)#	4.5 (2.3)	0.007

Post-Hoc comparison: * a-MCI vs HE, #Converters vs. Non-Converters; $p \leq 0.008$ Bonferroni corrected.

Abbreviations: a-MCI= amnestic Mild Cognitive Impairment; HE= Healthy Elderly; W-IR=15 Word List Immediate Recall; W-DR= 15 Word List Delayed Recall; W-HR= 15 Word List

Recognition Hit-rates; W-F= 15 Word List Recognition False; SS-IR= Short Story test Immediate Recall; SS-DR= Short Story test Delayed Recall

Supplementary Table 1. Results of factor analyses: total variance explained in patients with amnestic mild cognitive impairment.

Baseline: Total variance explained

Factor	Initial Eigenvalues			Extraction Sum of Squares Loadings#			Rotate Extraction Sum of Squares Loadings*		
	Total	% of Variance	% Cumulative	Total	% of Variance	% Cumulative	Total	% of Variance	% Cumulative
1	**2.51**	41.81	41.81	2.35	39.24	39.24	1.82	30.38	30.38
2	**1.46**	24.42	66.22	0.98	16.38	55.63	1.51	25.24	55.62
3	0.94	15.65	81.87						
4	0.66	10.99	92.87						
5	0.27	4.59	97.46						
6	0.15	2.54	100.00						

Follow-up: Total variance explained

Factor	Initial Eigenvalues			Extraction Sum of Squares Loadings#			Rotate Extraction Sum of Squares Loadings*		
	Total	% of Variance	% Cumulative	Total	% of Variance	% Cumulative	Total	% of Variance	% Cumulative

1	**3.31**	55.10	55.10	3.07	55.11	51.11	2.94	48.95	48.95
2	**1.30**	21.70	76.80	0.98	16.33	67.45	1.11	18.50	67.45
3	0.70	11.67	88.47						
4	0.38	6.33	94.80						
5	0.19	3.23	98.03						
6	0.12	1.97	100.00						

Extraction method: Maximum Likelihood; *Rotation method: Varimax with Kaiser Normalization

Supplementary Table 2. Factor analyses: Communalities and factor matrix in patients with amnestic mild cognitive impairment.

	Baseline			
	Communalities#		**Rotated Factor matrix***	
	Initial	**Extraction**	**Factor 1**	**Factor 2**
W-IR	0.35	0.35	0.07	0.59
W-DR	0.59	0.99	0.32	0.95
W-HR	0.36	0.23	0.08	0.47
W-F	0.27	0.12	-0.32	-0.12
SS-IR	0.68	0.64	0.80	0.08
SS-DR	0.74	0.99	0.98	0.18
	Follow-up			
	Communalities#		**Rotated Factor matrix***	
	Initial	**Extraction**	**Factor 1**	**Factor 2**
W-IR	0.55	0.36	0.57	0.32
W-DR	0.58	0.55	0.72	0.07
W-HR	0.70	0.61	0.63	0.78
W-F	0.57	0.99	-0.10	0.60
SS-IR	0.74	0.76	0.85	0.06
SS-DR	0.76	0.83	0.98	-0.17

Extraction method: Maximum Likelihood; *Rotation method: Varimax with Kaiser Normalization.

Abbreviations: W-IR=15 Word List Immediate Recall; W-DR= 15 Word List Delayed Recall; W-HR= 15 Word List Recognition Hit-rates; W-F= 15 Word List Recognition False; SS-IR= Short Story test Immediate Recall; SS-DR= Short Story test Delayed Recall.

Supplementary Table 3. Partial Least Squares analysis in patients with amnestic mild cognitive impairment.

Panel A	**Independent variable (X)**		**Dependent variable (Y)**		
Latent factors	**% of Variance**	**% Cumulative**	**% of Variance**	**% Cumulative**	**R^2**
1	**0.36**	**0.36**	**0.36**	**0.36**	**0.34**
2	0.17	0.54	0.01	0.37	0.33
3	0.25	0.79	0.01	0.38	0.31
4	0.13	0.92	0.01	0.39	0.29
5	0.08	0.99	0.01	0.40	0.27
Panel B	**VIP index**	**B-matrix**	**Weight**	**Loadings**	
Gender	0.53	-0.09	-0.22	-0.26	
Age baseline	1.12	-0.01	-0.46	-0.51	
Education	0.40	-0.01	-0.16	-0.11	
Age follow-up	1.08	-0.01	-0.44	-0.51	
MMSE baseline	**1.36**	**0.06**	**0.55**	**0.48**	
MMSE follow-up	1.13	0.02	0.46	0.43	

Supplementary Table 4. Results of factor analysis in healthy elderly individuals.

Total variance explained

Factor	Initial Eigenvalues			Extraction Sum of Squares Loadings#			Rotate Extraction Sum of Squares Loadings*		
	Total	**% of Variance**	**% Cumulative**	**Total**	**% of Variance**	**% Cumulative**	**Total**	**% of Variance**	**% Cumulative**
1	**2.28**	38.00	38.00	1.82	30.34	30.34	1.85	30.92	30.92
2	**1.94**	32.30	70.30	1.85	30.86	61.21	1.82	30.29	61.21
3	0.74	12.44	82.74						
4	0.64	10.78	93.53						
5	0.26	4.37	97.90						
6	0.12	2.09	100.00						

Communalities and factor matrix

	Communalities#		Rotated Factor Matrix*	
	Initial	**Extraction**	**Factor 1**	**Factor 2**
W-IR	0.56	0.76	0.88	-0.01

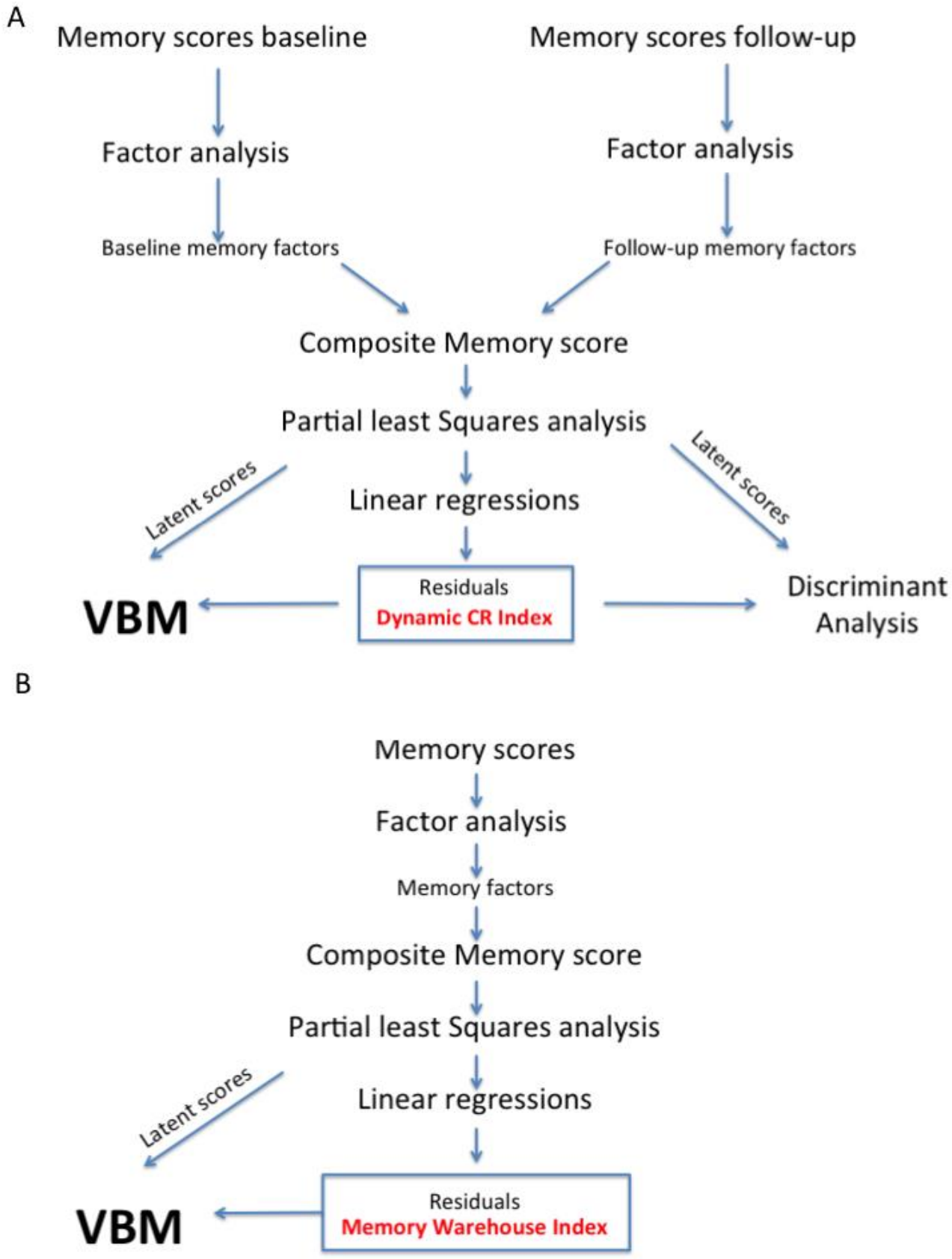
W-DR	0.56	0.70	0.82	0.17
W-HR	0.22	0.24	0.49	-0.06
W-F	0.18	0.21	-0.41	0.19
SS-IR	0.76	0.98	-0.03	0.99
SS-DR	0.76	0.77	-0.05	0.88

Extraction method: Maximum Likelihood; *Rotation method: Varimax with Kaiser Normalization

Supplementary Table 5. Partial Least Squares analysis in healthy elderly individuals

Panel A	**Independent variable (X)**		**Dependent variable (Y)**		
Latent factors	**% of Variance**	**% Cumulative**	**% of Variance**	**% Cumulative**	**R^2**
1	**0.40**	**0.40**	**0.22**	**0.22**	**0.20**
2	0.17	0.57	0.01	0.23	0.19
3	0.27	0.85	0.01	0.23	0.18
4	0.15	1.00	0.001	0.23	0.16
Panel B	**VIP index**	**B-matrix**	**Weight**	**Loadings**	
Gender	0.70	0.20	0.35	0.32	
Age	0.92	-0.02	-0.46	-0.48	
Education	0.80	0.01	0.40	0.50	
MMSE	**1.42**	**0.19**	**0.71**	**0.65**	

Figure 1.


A
Memory scores baseline
Memory scores follow-up
Factor analysis
Factor analysis
Baseline memory factors
Follow-up memory factors
Composite Memory score
Partial least Squares analysis
Latent scores
Linear regressions
Latent scores
VBM
Residuals
Dynamic CR Index
Discriminant Analysis
B
Memory scores
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Partial least Squares analysis
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Linear regressions
VBM
Residuals
Memory Warehouse Index

Figure 2.

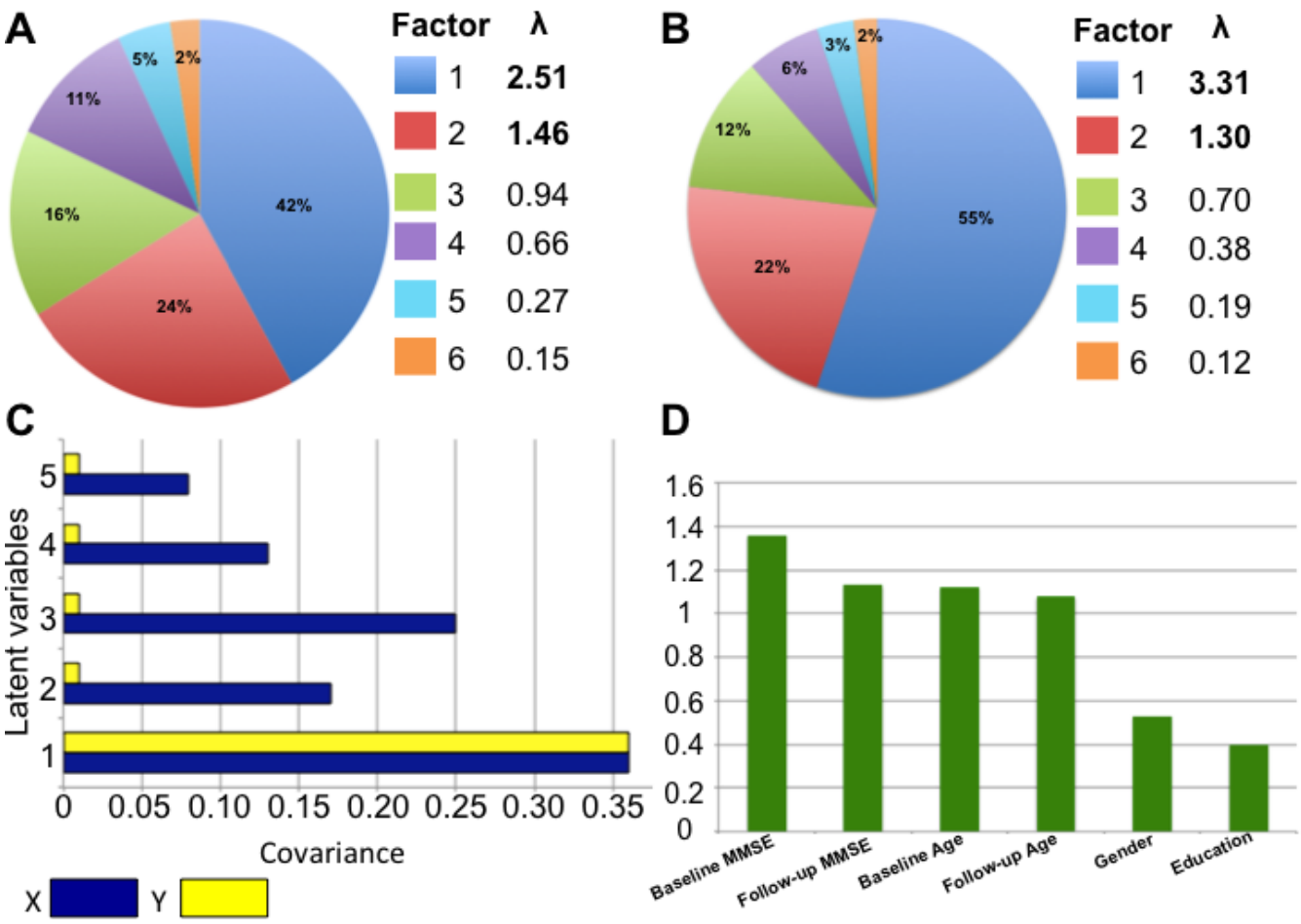

A
Factor λ
1 2.51
2 1.46
3 0.94
4 0.66
5 0.27
6 0.15
42%
24%
16%
11%
5%
2%
B
Factor λ
1 3.31
2 1.30
3 0.70
4 0.38
5 0.19
6 0.12
55%
22%
12%
6%
3%
2%
C
Latent variables
5
4
3
2
1
0 0.05 0.10 0.15 0.20 0.25 0.30 0.35
Covariance
X
Y
D
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Baseline MMSE
Follow-up MMSE
Baseline Age
Follow-up Age
Gender
Education

Figure 3.

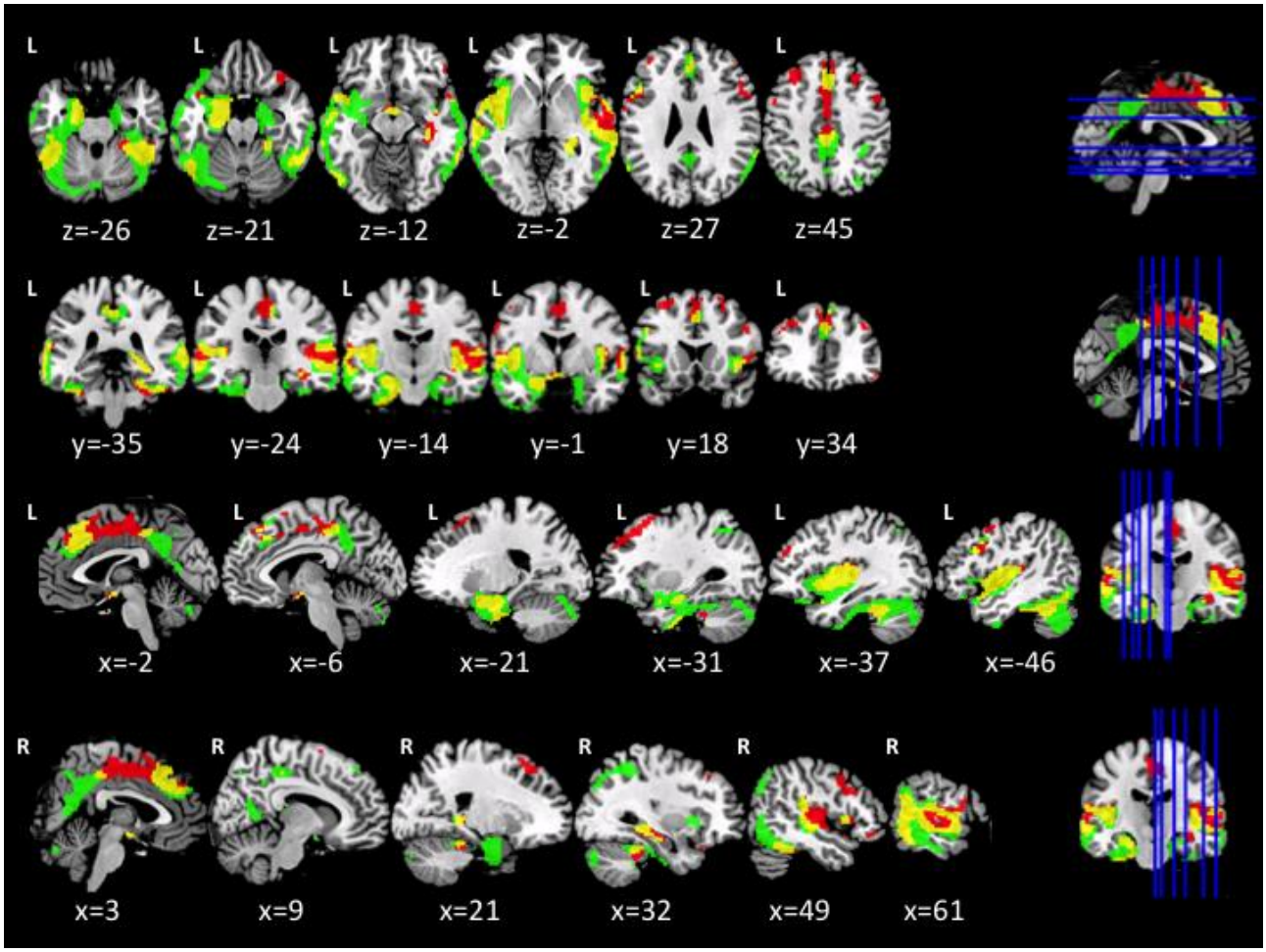

L
z=-26
z=-21
z=-12
z=-2
z=27
z=45
y=-35
y=-24
y=-14
y=-1
y=18
y=34
x=-2
x=-6
x=-21
x=-31
x=-37
x=-46
R
x=3
x=9
x=21
x=32
x=49
x=61

Figure 4.

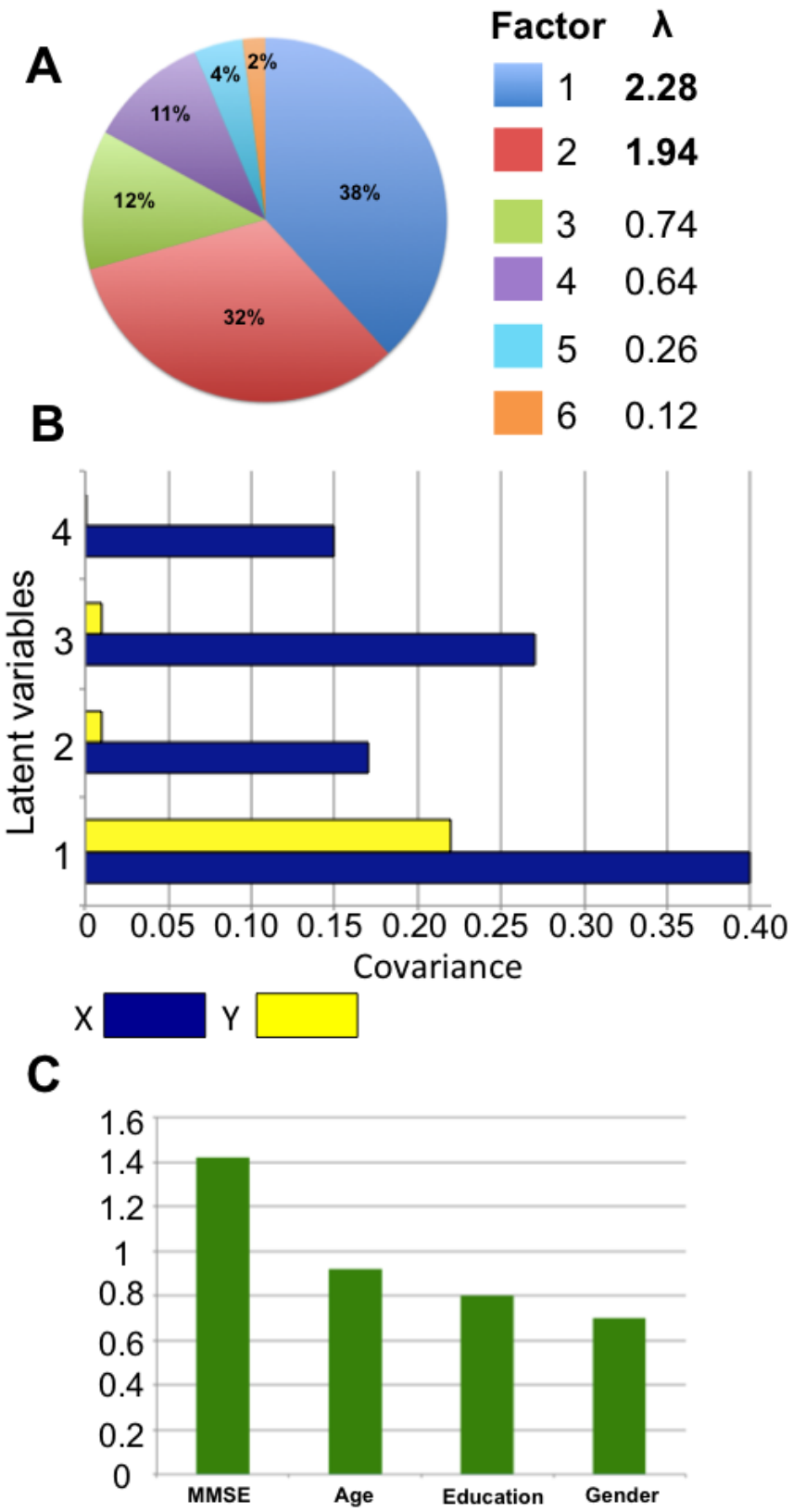
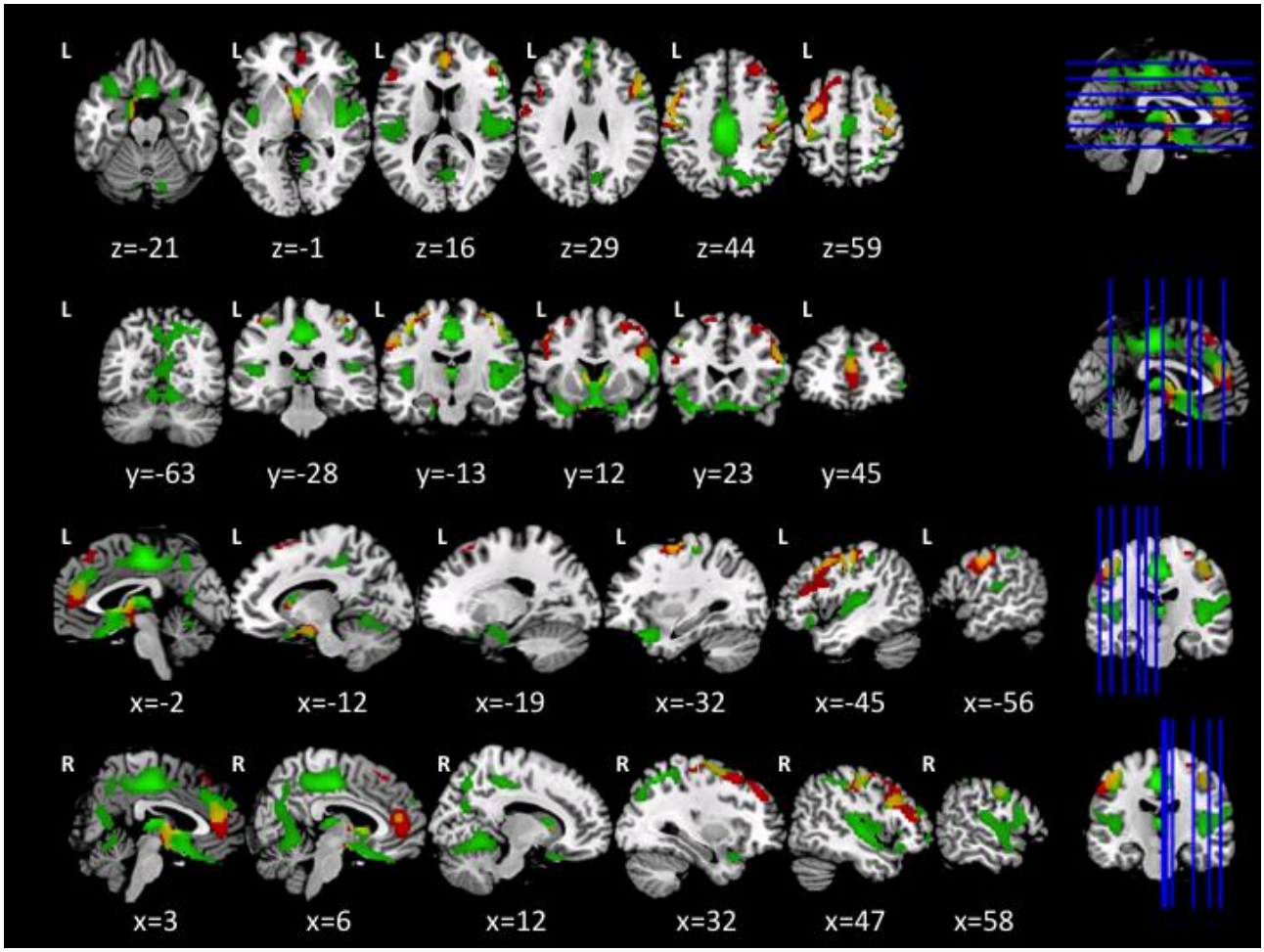

A
Factor λ
1 2.28
2 1.94
3 0.74
4 0.64
5 0.26
6 0.12
38%
32%
12%
11%
4%
2%
B
Latent variables
4
3
2
1
0 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40
Covariance
X
Y
C
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
MMSE
Age
Education
Gender

Figure 5.


L
z=-21
z=-1
z=16
z=29
z=44
z=59
y=-63
y=-28
y=-13
y=12
y=23
y=45
x=-2
x=-12
x=-19
x=-32
x=-45
x=-56
R
x=3
x=6
x=12
x=32
x=47
x=58